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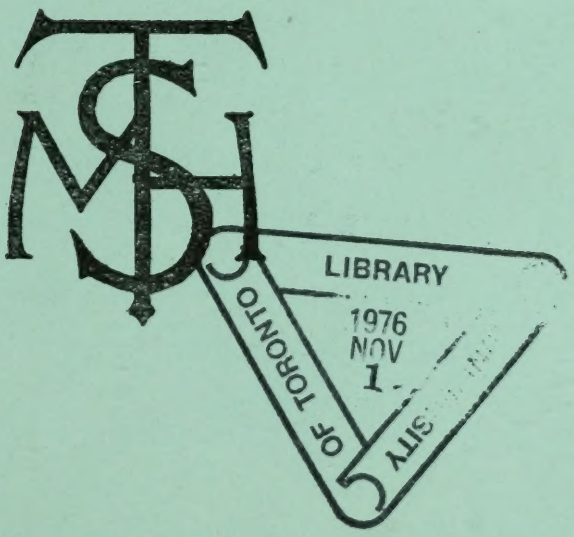
Vol. VI. No. 5. April, 1913.

TRANSACTIONS

OF THE

SOCIETY OF TROPICAL MEDICINE AND HYGIENE.



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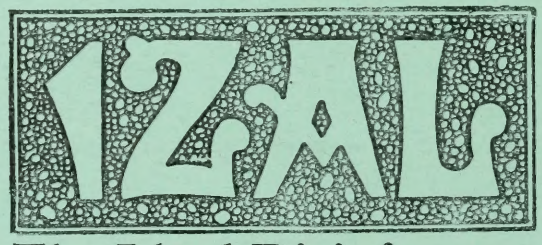
Non-Poisonous.  **Non-Corrosive.**

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APRIL, 1913. VOLUME VI. NO. 5.

CONTENTS.

	PAGE
Is Pellagra a Disease due to Deficiency of Nutrition? By F. M. SANDWITH, M.D., F.R.C.P.	143
Fatal Pellagra in Two English Boys, with the Results of the Pathological Investigation of one case By CHARLES R. BOX, M.D. and F. W. MOTT, F.R.S. (Illustrated.)	149
The Histological Changes in the Nervous System of Dr. BOX'S case of Pellagra, compared with changes found in a case of Pellagra dying in the Abassieh Asylum, Cairo. By F. W. MOTT, F.R.S.	157
Report of Egyptian Case. By Dr. R. W. J. PEARSON	161
Discussion: Dr. A. J. CHALMERS, Dr. J. M. MACLEOD, Mr. CASIMIR FUNK, Sir R. HAVELOCK CHARLES, Dr. F. M. SANDWITH, Dr. C. R. BOX, Dr. F. W. MOTT	163
Notes and Comments:	
Budding and other changes described by SCHAUDINN for *E. histolytica* seen in a race of *E. tetragena*. By S. T. DARLING ...	171
The Nature of Zambesi Fever. By W. J. BRUCE, M.R.C.S., Vicenti, Zambesi, Portuguese East Africa	173
The Etiology of Blackwater Fever, etc. By A. G. NEWELL, M.D., D.P.H., Lahore	177
The Etiology of Blackwater Fever. By H. STANNUS STANNUS, M.D., Nyasaland	181

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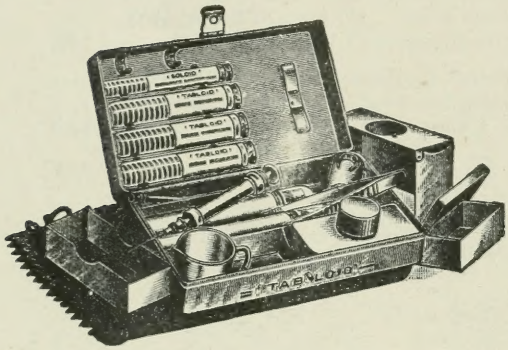

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TRANSACTIONS
OF THE
SOCIETY OF TROPICAL MEDICINE AND HYGIENE.

APRIL, 1913.
VOLUME VI. No. 5.

Proceedings of a Meeting of the Society on Friday, February 21st, 1913.
SIR WILLIAM LEISHMAN, F.R.S., *President*, in the Chair.

IS PELLAGRA A DISEASE DUE TO DEFICIENCY OF NUTRITION?

By F. M. SANDWITH, M.D., F.R.C.P.

The student approaching to-day for the first time the pellagra question encounters many theories relating to the etiology of the disease of which at least three are prominent.

1. He will learn that STRAMBIO[1] drew attention to the fact that in the districts of Lombardy, where the disease was endemic, most of the cases occurred in those villages where polenta of maize constituted more or less exclusively the food of the inhabitants. During the 127 years which have passed since STRAMBIO was placed in charge of the earliest pellagra hospital, there have never been wanting believers that pellagra and maize were in some mysterious way connected, and numerous unsuccessful efforts have been made to prove that some special fungus or mould in bad maize is the true *causa causans* of the disease.

It is, perhaps, interesting to note that in STRAMBIO'S time many writers confused pellagra with scurvy. He himself said that scurvy closely resembled pellagra, and that the filthy and unhygienic habits of the peasants predisposed to both diseases.

2. The student is told of the photodynamic theory of RAUBITSCHEK,[2] that the disease is produced by the patient subsisting on a diet of either good or bad maize (and perhaps other cereals) provided he is brought under the influence of sunlight.

This is a modern adaptation of the views of FRAPOLLI[3], who was

apparently the earliest writer to hold that the action of the rays of the sun was the sole factor in the causation.

3. He may be fascinated by the theory advanced by Dr. SAMBON in 1905, that the disease belongs to the protozoal group and may be conveyed to man by a biting insect. During the last seven years many workers have looked with a favourable eye upon this brilliant theory, partly because they are tired of the seemingly unprofitable maize controversy, and partly because the etiological pendulum has been successfully swinging for the past 30 years in the direction of discovering a specific micro-organism for so many diseases. Moreover, almost every year of the present century has proved to us the fresh importance of insect carriers.

Since the end of the 18th century, when ZANETTI[4] and GHERARDINI[5] thought that bad food, aided by absence of hygiene, was the definite cause of pellagra, this theory has often been discussed. The recent developments in connection with beri-beri have caused me to wonder anew whether we have not here to deal with another disease due to deficiency of nutrition.

I therefore ventured to express this view in a paper I was asked to contribute to the Conference on pellagra held in Columbia, South Carolina, in October, 1912.

In thus reviving an almost defunct theory I am not unmindful of the harsh criticism of a German author who has recently written that "the field of pellagrous etiology has been the playground of scientific fledglings, whose intellectual judgment is befuddled because they have no real comprehension of the fundamental question, and therefore attempt to introduce into the etiology of pellagra all sorts of things, from bald banalities to the most wonderful fantasies!"

The history of beri-beri and pellagra has some points of resemblance. In both the climate, weather, soil, constitution and mode of living have been blamed, while scurvy and malaria have been confused with each of them. Cockroaches, lice and other insects have been suspected as the carriers of beri-beri, while many bacilli, cocci and spores have been thought to be of supreme bacteriological importance. Both diseases have been thought to be due to protozoa, but in neither of them has any one succeeded in generating the disease in animals by means of blood freshly drawn from patients.

In both diseases gastric symptoms appear early; they are both non-contagious; occur chiefly in young adults and are made worse by any co-existing acute illness; both are known to haunt institutions, such as lunatic asylums; and both are subject to periodical fluctuations. Predisposition to the two diseases is not extinguished by recovery, on the contrary, the convalescent is apt to be attacked again, sometimes every year for a long period of time.

Authors who wrote from the East Indies (British and Dutch) and from Japan, were the first to suggest that beri-beri was caused by an insufficient diet, or a diet not corresponding to the needs of the body. This was firmly believed again by VAN LEENT and others who saw many cases, both among Europeans and natives, during the Atcheen war, which began in 1873. Since 1885 beri-beri has been practically eradicated from the Japanese navy by improving the rations, diminishing the rice and fish, and adding meat, fresh vegetables, sugar, beans, barley, milk, salt, etc.

I take this opportunity of shewing some of the striking diagrams which were given to me by Baron TAKAKI. Our knowledge as to why certain rice is deficient in nutrition is now still further advanced, and most of us are converts to this etiological view. Thanks to the production of an analogous disease in birds, we now believe that tropical beri-beri (at least in the Malay Peninsula), can be prevented by using unmilled rice, and that early cases can be cured of it and of infantile beri-beri (in Manila) by adding to the diet that part of the rice which has been removed during milling.

Now I have always found that *early* cases of pellagra in Egypt can be cured by admitting them to hospital (where they gain in weight) and giving them the ordinary mixed diet, which included meat and excluded maize, and was distinctly a better diet than the one the patients had been subsisting on before admission. It is true that many of these patients again became pellagrous when they returned to their homes and maize food.

Why beri-beri patients suffer from peripheral neuritis and why early pellagra is followed by central neuritis and disease of the brain and spinal cord we no more know than why a deficiency of vegetables or fruit sometimes produces scurvy and a deficiency of animal fat causes rickets in young mammals.

These are questions which chemical pathologists may some day be able to answer, but not until micro-chemical analysis has greatly advanced.

In the meantime physiology teaches that proteids are absolutely necessary for the continuance of life and they cannot be satisfactorily replaced in the diet by any other dietary constituent, either organic or inorganic. It is true that an animal organism can exist for a period of time without proteids, but this is only existence, not normal life. Proteids alone repair the tissue-waste, and if they are not present in the diet in proper proportion the tissues feed on themselves.

Of the protein decomposition products the amino-acids are pre-eminently the most important class. Among the products is the necessary tryptophane $C_{11}H_{12}N_2O_2$ or indol-a-amino-propionic acid.[6] "Tryptophane is the mother-substance of indole, skatole, skatole acetic acid and skatole carboxylic acid, all of which are formed as secondary decomposition products of proteins." Now tryptophane is present in nearly all proteids, but has been shewn to be *entirely absent from zein*, which is the proteid of maize, and belongs to the same group as the *hordein* of barley, the *gliadin* of wheat and rye, and the *bynin* of malt.

It has been found by physiologists that tryptophane must be given pure to animals, because the animals have no power of synthesising the necessary tryptophane from any of its break-down products. The best maize *(zea-mays)* has a higher proteid value than rice, but it is quite possible that the inferior or damaged maize eaten by peasants in Italy and Egypt may contain some complex organic body which, by virtue of a slight chemical change, cannot be used in the normal chain of living processes. If this be true, it would follow that the more essential organs, such as the heart, would take as much of these necessary chemical bodies (tryptophane etc.) as they require. This can only be done by robbing other parts of the body and may possibly account for the degenerative changes so well known in the brain and spinal cord of advanced and fulminating cases of pellagra.

Although the changes undergone by a substance within the human body may differ from those which we see in a laboratory, yet the effects of the substance must ultimately depend on its chemical composition. The degree of chemical affinity for the tissues of the body is important; for instance, atoxyl, a "para" salt, is effective against trypanosomes,

while, according to BREINL and NIERENSTEIN, its "meta" and "ortho" cousins are of little or no value.

It is well known that drugs have an elective power for certain parts of the body and even for certain muscles. Nicotine, for instance, in minute concentrations, affects the rectus abdominis of frogs, whereas only strong concentrations will affect ordinary skeletal muscles, such as the sartorius. There must surely be some chemical difference between muscles which appear microscopically to be similar. Again, curare in very small doses paralyses the neuro-muscular junction of skeletal muscles, but has no effect on unstriped muscle and has no influence on the transference of impulses in the central nervous system.

Minute chemical changes may abolish the specific action of certain bodies, as an illustration of which it is well known to physiologists that adrenalin is efficient in only one optically active form. This form, left under certain conditions, will become an optically inactive mixture with only 50 per cent. of the original body left, so that the physiological efficiency is diminished by 50 per cent.

Ultra violet rays have the effect of accelerating most organic chemical reactions and may even bring them to different final points, upsetting the balanced action between them; for instance, chlorine and hydrogen, left together in the dark, will take ages to combine, but in the presence of sunlight they may combine explosively. Can this chemical fact throw any light upon the oft repeated observation that pellagrous erythema usually appears for the first time during the spring months when the ultra-violet rays of the sun are specially strong?

I should like to add to these rather disjointed observations that it is by no means certain that rice is the only cereal which can produce that deficiency of nutrition which causes the clinical picture of tropical beri-beri.

Similarly it must not be assumed that maize is the only cereal which, under certain conditions, can cause pellagra. If this be conceded it would help us to understand rare cases of pellagra which occur in countries where maize is not the chief cereal consumed.

While writing this paper I have received a copy of the complete Report of the Pellagra Commission of the State of Illinois[7] which has been working at the pellagra problem during the last three years, and I have naturally looked to see whether the findings of the Commission throw

any light upon the possibility of pellagra being a disease due to deficiency of nutrition.

In the urine of the pellagrous patients examined nothing very decisive was found "with the exception of a very marked indican reaction which was present in all," and "evidence of great disturbance in metabolism."

Attention is drawn to the gastro-intestinal symptoms and the consequent progressive emaciation and exhaustion.

A feeding experiment was conducted at the Peoria Asylum, where 60 patients who were non-pellagrous, chronic lunatics, were fed for twelve months on a generous maize diet, while 60 similar cases were fed on a maize-free diet. At the end of the time the maize eaters had four certain and one doubtful case of pellagra, while the maize free group included five certain and five doubtful cases of pellagra. This experiment, so far as it goes, is certainly not in favour of the deficiency of nutrition theory, but it must be pointed out that the patients fed on maize were also given meat every day, and for four days in the week they had milk too. This was, therefore, a much better diet than the poorest peasants in Italy and Egypt subsist upon, for they eat practically no meat, fish, milk or eggs.

The Commission points out "that the number of cases of pellagra have diminished at Peoria and Dunning (asylums) coincidentally with increased meat and have increased at Elgin (asylum) with diminished meat."

While the Commission concludes that "according to the weight of evidence pellagra is a disease due to infection with a living micro-organism of unknown nature," it also states that deficient animal proteids in the diet may constitute a predisposing factor in the contraction of the disease. The Commission therefore recommends "that as a prophylactic measure the animal protein content of the State Hospital dietaries be increased."

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FATAL PELLAGRA IN TWO ENGLISH BOYS, WITH THE RESULTS OF THE PATHOLOGICAL INVESTIGATION OF ONE CASE.

By CHARLES R. BOX, M.D. and F. W. MOTT, F.R.S.

On September 20th, 1912, a lad, E.T. of eight was admitted to St. Thomas's Hospital under the care of Dr. Box. The parents feared that he was developing an obscure nervous disease similar to one which had affected his brother for several years, and finally carried him off at the age of thirteen in the year 1911.

The present patient was born at Leyton, in Essex; later resided for five years at Catford, in the suburbs of London, and finally removed with his family to Slough. His father and mother are English and not related to each other. His father is an army pensioner, and for the last eighteen months has suffered from aortic disease. The mother is quite healthy.

Besides the patient they have had nine children. Five of these are living. One died of laryngeal diphtheria; one of an acute toxæmia, after an illness of 24 hours; and one, to whom reference will be made later, from an illness which was no doubt pellagra.

The patient's nervous symptoms were first noticed in June, 1912, three months before he came under observation, when he "fainted" whilst playing cricket. The "faints" recurred on several occasions. Later on twitching movements of the limbs were noticed and also a transitory convergent squint.

On Bank Holiday, August 5th, there occurred a new sort of seizure. He had been stooping and suddenly stood erect, threw his head backwards and would have fallen if not caught. The body became rigid but consciousness was not lost. Similar attacks recurred several times, always with a premonitory feeling of giddiness. He had never bitten his tongue nor been observed to foam at the mouth.

Recently he had become more and more unsteady in his movements.

On examination the boy appeared to be of average intelligence. His

memory was good and he answered questions readily, but proved to be of an emotional disposition and easily moved to tears. His weight was 43 lbs., or 9 lbs. below the average for his age. His father attributed this to the failure of his appetite, saying that there was always plenty of food for the family.

He was able to walk, but his gait shewed a mixture of spasm and ataxy. He moved stiffly with his legs wide apart. The feet were raised high from the ground, steppage fashion, and there was a decided tendency to stagger, this being increased by closure of the eyes. Later adductor spasm also declared itself.

On the day of admission, whilst his gait was being investigated, he had one of the seizures which had been described by his parents. His head was stiffly retracted, he became rigid and would have fallen backwards if not prevented. The attack lasted for a few moments only and consciousness was not lost. He cried quietly all the time.

A coarse nystagmus which accompanied all movements of the eyes was always present, and his speech was rather indistinct. These were the only abnormalities of the cranial motor mechanism. The pupils were active and equal. The optic papillæ were quite healthy. Hearing, vision, taste and smell proved to be normal.

Even when lying in bed the muscles of the arms and legs, particularly the latter, were in a condition of moderate rigidity, but they were not wasted, and there was no appreciable weakness. All movements appeared stiff.

It was also evident, particularly when he was being photographed, that irregular, spasmodic movements of small range were apt to appear both in face and limbs, producing slight jerks which suggested the effect of a faradic shock. There were no deformities of the feet or hands, and the spinal column was straight.

All the deep reflexes, both in arms and legs, were increased but no clonus could be elicited. The plantar reflex was always flexor in type. The cremasteric, abdominal, epigastric and corneal reflexes were present.

Sensibility to all forms of stimuli was unimpaired. Subsequently Dr. SANDWITH pointed out that there appeared to be some para-vertebral tenderness which could be elicited by making firm pressure alongside the vertebral spines, on the right side from the second to the

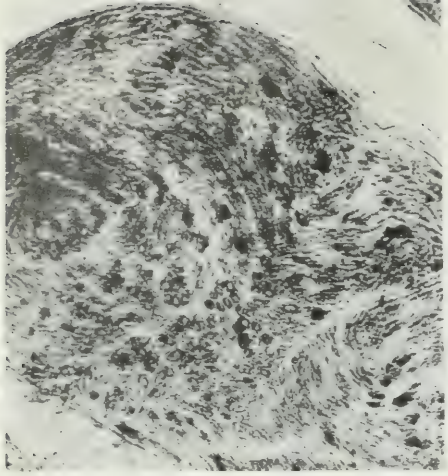

Fig. 1.—Trans. Section—Sciatic Nerve.
Marchi Method. *Mag. 120.*

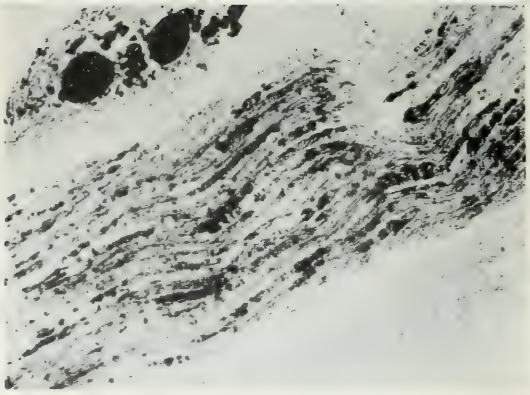

Fig. 2.—Longt. Section—Sciatic Nerve.
Marchi Method. *Mag. 160.*

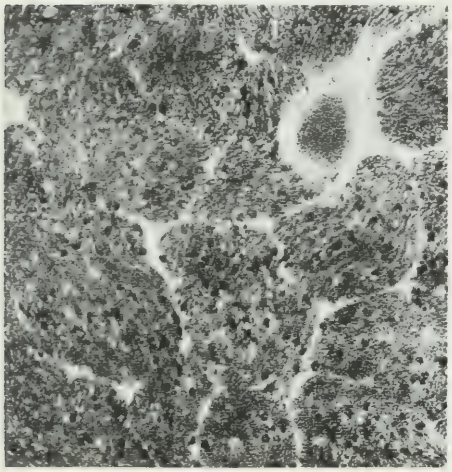

Fig. 3.—Cauda Equina.
Marchi Method. *Mag. 80.*

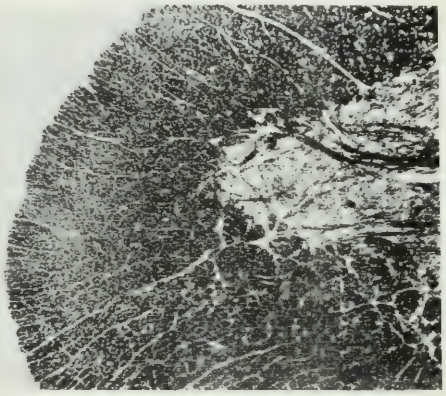

Fig. 4.—Spinal Cord—Cervical Region. Cerebellar Tract.
Weigert-Pal. Method.

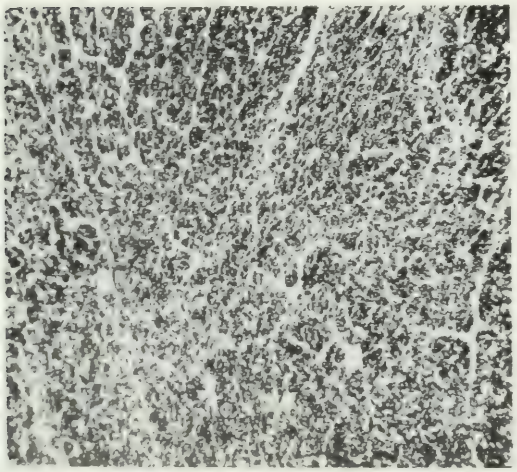

Fig. 5.—Spinal Cord—Cervical Region. Cerebellar Tract.
Weigert-Pal. Method. *Mag. 80.*

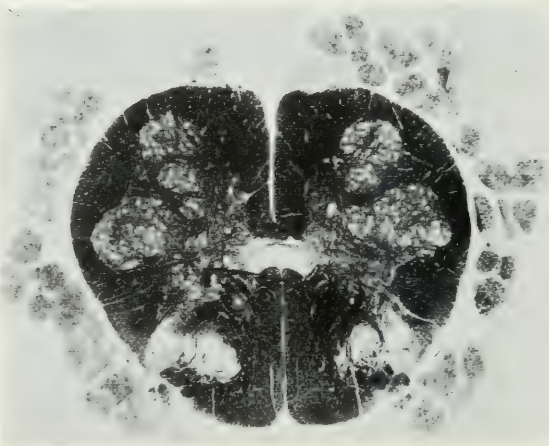

Fig. 6.—Spinal Cord—Lumbar Region.
Weigert-Pal. Method.

ILLUSTRATIONS TO ACCOMPANY PAPER BY

Fig. 7.—Spinal Cord—Cervical Region.
Weigert-Pal. Method.

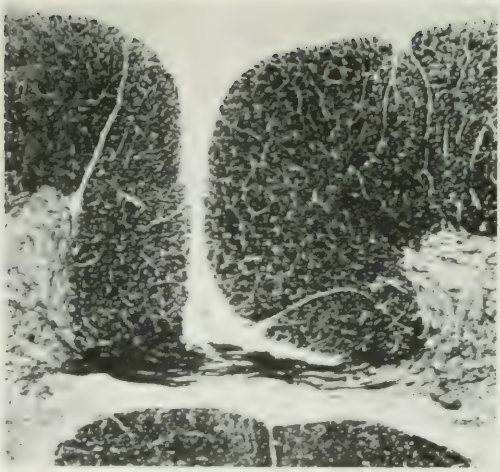

Fig. 8. Direct Pyramidal Tracts—Cervical Region.
Weigert-Pal. Method

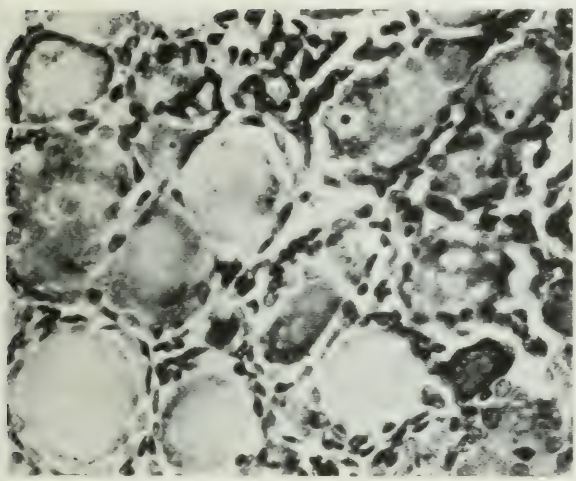

Fig. 9. Posterior Spinal Ganglion.
Polychrome Blue Method. Mag. 280.

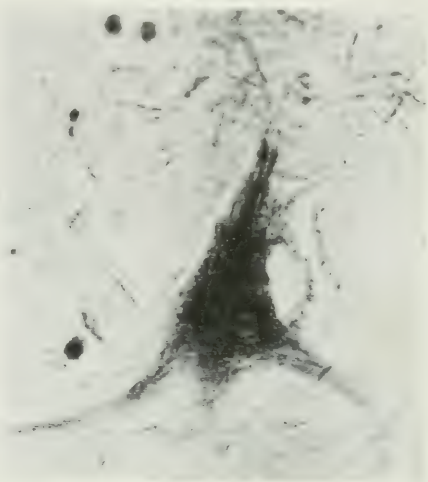

Fig. 10.—Betz Cell—Motor Cortex.
Cajal Method. Mag. 700.

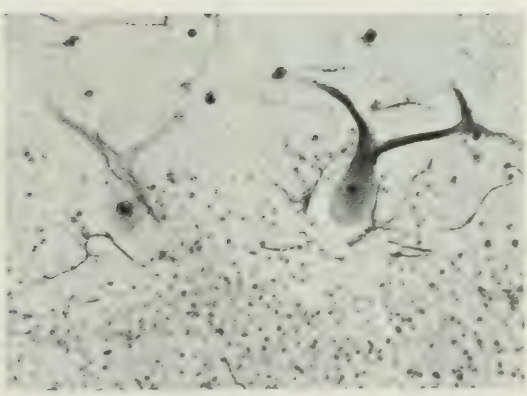

Fig. 11.—Purkinje Cells (Cerebellum)
Bielschowsky Method. Mag. 300.

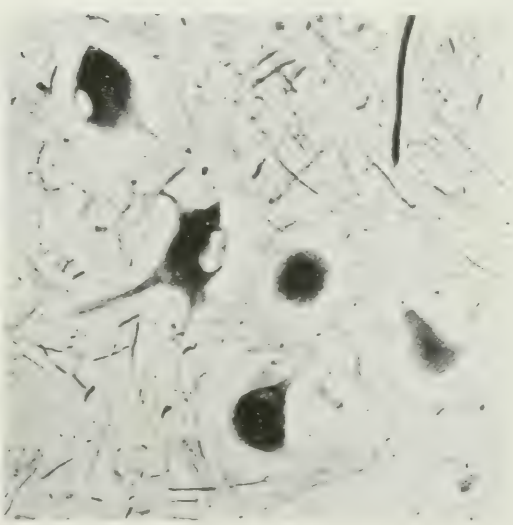

Fig. 12.—Anterior Horn Cells
Bielschowsky Method Mag. 350.

R. C. R. BOX AND DR. F. W. MOTT.

From microphotographs of Dr. MOTT'S specimens

ninth dorsal, and on the left from the seventh cervical to the fourth dorsal.

The boy swallowed both solids and liquids with ease, but all the time he was under observation there was incontinence of both urine and fæces.

With regard to the alimentary system there was an insignificant rawness of the edges of the tongue and an inflammatory condition of the skin immediately surrounding the anus. The appetite was very capricious and the bowels were inclined to be loose, being opened two or three times a day; later there was a more decided tendency to diarrhœa. The cardio-vascular and respiratory systems shewed no signs of disease. The urine contained neither albumen nor sugar.

The patient presented, in addition to his nervous symptoms, a symmetrical erythematous dermatitis of striking distribution which afforded the clue to the diagnosis of his disease. The skin inflammation involved the backs of the hands and wrists, the orbital regions and bridge of the nose, the nape of the neck and backs of the ears, and, to a slight degree, the points of the elbows.

On the face the dermatitis crossed the bridge of the nose, encircled both eyes and spread slightly on to the malar regions. The skin over this area was reddish in colour, resembling acute sunburn. It was somewhat thickened and shewed a decided tendency to desquamate in small branny scales. The eyelids were slightly swollen and conjunctivæ were injected, presenting a lachrymose appearance. The skin of the nape of the neck was less red and rather more scaly, the lateral extensions of the dermatitis behind the ears and to the adjacent mastoid regions were quite symmetrical. The hair of the back of the scalp was dry, lustreless and thin.

The eruption on the hands had a rougher appearance. When viewed from the dorsal aspects it terminated by a sharp margin across the arm, four finger breadths above the wrist. It covered the backs of both hands, extended on to the fingers in less marked form, and on the dorsum of each terminal phalanx assumed a brownish tint which was in marked contrast with the red colour of the rest of the affected area. The nails were healthy but shallow ulcerations were found in several of the interdigital clefts.

The palms of the hands escaped, but the dermatitis shewed a ten-

dency to extend from the dorsum of the wrists across the palmar aspects, especially from the radial side.

At the points of the elbows a brown scaliness of the skin was evident, and, although there was no red eruption on the feet or legs, the skin of the front of each leg when lightly rubbed assumed a very powdery appearance.

When he was first admitted the affected skin had a fairly bright red appearance, but the colour gradually faded to a brownish tint. At no time did he appear to experience either pain or irritation in the affected parts.

The eruption was recognised as pellagra, owing to its resemblance to the photographs in Drs. LAVINDER and BABCOCK'S translation of Dr. MARIE'S book on the disease. A copy of this work had been presented to Dr. BOX by Dr. J. J. WATSON, of Columbia, who visited England in 1910.

As the result of lumbar puncture, 15 c.c. of clear cerebrospinal fluid were withdrawn. The pressure was not increased. The fluid was examined in the clinical laboratory of the hospital, under the direction of Dr. L. S. DUDGEON. No cells were seen, no globulin was found, and the Wassermann reaction was negative.

At the same time the blood was also examined. This also gave a negative Wassermann reaction, and the count was as follows:—Erythrocytes, 3,475,000 per c.m.; hæmoglobin, 65 per cent.; colour index, 0·9; leucocytes, 5,140 per c.m.

Differential count:—Polynuclears, 59·5 per cent.; polynuclear eosins, 1·75 per cent.; small lymphocytes, 28·5 per cent.; large lymphocytes, 5 per cent.; large hyaline cells, 5·25 per cent.

Whilst under observation in the hospital on some days the patient was decidedly more tremulous than on others. Shock-like twitches of the muscles of the face, arms and legs continued to appear. There were no more cerebral seizures, but a tendency to adductor spasm was superadded to the first observed extensor rigidity of the legs. Spasm of the calf muscles also caused a tendency to walk on the toes. The knee jerks remained exaggerated, but no extensor response was ever obtained from the soles, and no true clonus appeared.

The patient vomited on one or two occasions and the appetite was variable, but, notwithstanding this, he put on weight during the first

week, only to lose it again later as he became progressively weaker.

The state of the bowels, tending to increasing looseness, has already been mentioned.

During the latter part of his life he developed slight delusions, believing, among other things, that his father was under his bed.

Until the last three days of life his temperature was practically normal, only rising slightly on one or two occasions.

About a fortnight before death an acute suppurative balanitis made its appearance, but it ultimately became necessary to slit up the prepuce. This was effected under nitrous oxide anæsthesia three days before he died. The patient was very stuporous afterwards, but did to a certain extent regain consciousness. Whilst in this condition the knee jerks remained exaggerated, and a pseudoclonus was obtained at the ankle, but no extensor response from the soles. The jerky movements of the limbs continued to occur at intervals. The pulse now became accelerated and began to fail, whilst respiration was very irregular.

The day after the anæsthetic the temperature rose to 101·6, but soon fell to normal. The next day it barely touched 99·5. On the third day it ran up to 100·4, and the pulse rose to 160. After a short stage of irritability the patient died. The duration of illness was four months.

A post-mortem examination was carried out two and a half hours after death.

The body was not greatly emaciated. Fat was still present in the subcutaneous tissues and in the omenta.

The eruption could still be recognised on the hands and wrists, the elbows, the neck and the face, as a brownish scaly thickening.

The mouth, fauces and tongue shewed no macroscopic lesions. The lower third of the interior of the gullet was bile-stained, but the mucous membrane appeared normal. The gastric mucosa was coated with adherent mucus, but not injected, ulcerated or wasted.

The only striking point in connection with the small intestine was the quantity of mucus present in it.

The edges of the ileo-cæcal valve were purple in colour and superficially ulcerated; the ulceration extended on to the adjacent wall of the cæcum. In the colon itself, near the splenic flexure, was a circular cicatrix, about half an inch broad, and slightly ulcerated at its margin.

The appendix was normal in its proximal two-thirds. A tight

stricture had caused the distal third to become bulbous. It contained inspissated pus.

The mesenteric glands were enlarged; one or two of them contained caseous material which was calcifying. The largest glands were not much bigger than peas.

There was no peritonitis, either old or recent.

The liver was fatty-nutmeg in appearance and not enlarged. The gall-bladder contained dark bile. The weight of the liver was 24 ounces.

The spleen weighed $2\frac{1}{4}$ ounces. It was normal in colour, and the cut surface presented nothing remarkable.

The adrenals and pancreas appeared quite healthy.

The kidneys weighed $6\frac{1}{2}$ ounces. They were a little swollen, and on section had a pale œdematous appearance. Their capsules could be stripped readily.

The bladder, ureters and rectum were healthy. The prepuce had been slit dorsally, and was somewhat thickened from recent inflammation.

The pleuræ and pericardium were free from inflammation or adhesions.

The right and left lungs weighed 4 and 5 ounces respectively. They were slightly over-inflated and everywhere crepitant. No tubercles were found in lungs or bronchial glands.

The heart weighed $2\frac{3}{4}$ ounces. It was free from valve lesions and its muscle dark and firm.

The marrow in the femur and ribs was bright red.

The dura mater was healthy, as also were the great venous sinuses of the brain.

The pia-arachnoid was not œdematous and shewed no signs of opacities. The spinal meninges also were healthy.

The ventricles of the brain were not distended, and it was difficult to be sure of any sclerosis of the cord before hardening.

A culture made from the blood immediately after death shewed, according to Dr. DUDGEON'S report, the presence of streptococcus pyogenes.

History of the brother's fatal illness.—R.T., age eleven years, was admitted to St. Thomas's Hospital under the care of Dr. Box, on September 27th, 1910, and remained under observation for a fortnight

only. He was the sixth child of the family and, unlike his brother, was born in Kilkenny, but only resided there for five months, the family leaving that part thirteen years ago and removing to Essex.

For several years, possibly six, he had been getting weak on his legs, and was dull and backward with his studies. He suffered with incontinence of urine. Latterly he had become worse in every way and for a few weeks his speech had been indistinct.

In hospital he mostly lay curled up in his bed. His mental condition was dull. He was very slow to answer questions and easily moved to laughter. His voice was low-pitched, and he said he could not speak loudly.

There was marked weakness of both arms and legs, but no picked-out atrophy of muscles. There was also a tendency to spasticity, particularly in the lower limbs.

When he attempted voluntary movements with the hands a coarse intention tremor was noticeable. When he tried to walk his movements were very unsteady; he shewed a marked tendency to sway laterally and almost over-balanced when he turned round.

Movements of the eyes were not limited in any direction, but lateral movements were accompanied by a coarse nystagmus. The optic papillae, fundi and media were quite normal, but a high degree of hypermetropia was present in both eyes. The pupil reactions were sluggish but complete

All the arm reflexes were decidedly brisk. The knee-jerks were exaggerated, especially on the right side. No clonus was obtained in the lower limbs, but the plantar reflexes were both extensor in type and there was a double claw-foot.

Deglutition was normal. With regard to micturition, sometimes the urine was retained, sometimes there was incontinence.

No defect in cutaneous sensibility could be discovered.

The chest was well-formed and its movements good. No pulmonary disease was found.

The heart's area was not increased. There were no murmurs. The pulse was regular and varied from 72 to 96.

The temperature was normal throughout.

The only anomaly in the digestive system lay in the action of the bowels. At first these were constipated and enemata necessary. Later

there was a somewhat troublesome diarrhoea which needed treatment.

The blood was examined for a Wassermann reaction with negative result, and the cerebro-spinal fluid showed no globulin and no Wassermann reaction. Not enough for a cell count was obtained.

But little is known about the eruption. It was not specifically described in the notes, or indeed specially noticed in hospital, but in the state on admission he is described as being of a high colour and somewhat tuberculous facies, whilst later a compound tar ointment was prescribed, presumably for the face. We have since learned from his mother that he did have a rash which appeared three or four years before he came under observation at the hospital; that this rash appeared in the summer only on successive years; but that it was not so pronounced as the rash in his brother's case. It involved the face, neck and the hands, but did not cause any septic spots between the fingers.

The boy was discharged in fourteen days in much the same condition as when admitted, the disease being diagnosed as an anomalous form of combined degeneration of the cord in some respects resembling Friedreich's Ataxy. No suspicion of pellagra arose at the time.

We heard later that he died in January, 1911, but could not ascertain from the parents the immediate cause of his decease. The duration of illness was over six years. No post-mortem examination was made.

Both boys were said to be fond of "pop-corn," or parched maize, but only had means to buy it occasionally.

THE HISTOLOGICAL CHANGES IN THE NERVOUS SYSTEM OF DR BOX'S CASE OF PELLAGRA COMPARED WITH CHANGES FOUND IN A CASE OF PELLAGRA DYING IN THE ABASSIEH ASYLUM, CAIRO.

By F. W. MOTT, F.R.S.

METHOD EMPLOYED FOR PREPARATION OF SPECIMENS.

The brain, spinal cord, and a few of the posterior spinal ganglia and a small piece of the sciatic nerve were sent for examination. Portions of tissue obtained from various parts of the central nervous system were separately hardened and fixed in Muller's fluid for subsequent examination by the Marchi method for recent degeneration, and by the Weigert and Weigert Pal methods for fibre system degenerations. Other portions were hardened for a few days in 5 per cent. formalin, and transferred to alcohol in successive strengths for examination by Nissl method; some portions of the formol fixed tissues were subjected to the Bielschowsky method for demonstration of fibril changes in the cells.

The Muller hardened tissues were treated by the celloidon method before sections were cut by the Jung microtome.

The formol hardened specimens were embedded in paraffin and cut in the Cambridge rocking microtome. The sections were 10μ in thickness.

CHANGES OBSERVED IN THE FIBRES BY THE MARCHI METHOD.

Sciatic Nerve.—Recent scattered degenerated fibres were found in all the longitudinal and transverse sections of the sciatic nerve; not limited to any bundle of fibres, but general, though somewhat unequal in numbers in all. *Fig. 1* shews one of these bundles in transverse section; the black dots are the degenerated fibres. *Fig. 2*, a bundle in longitudinal section. Owing to the piece of nerve not having been pinned out on cork when placed in the hardening fluid before I received it the fibres are curled, consequently the sections have cut many of the fibres obliquely.

Cauda Equina.—The roots of the *cauda equina* shew similarly scattered degenerated fibres *(vide Fig. 3)*.

Spinal Cord.—There is general diffuse and scattered degenerated

fibres throughout the white matter, more marked in the postero-lateral and posterior median columns than elsewhere.

CHANGES OBSERVED IN THE FIBRE SYSTEMS BY THE WEIGERT AND WEIGERT PAL METHODS.

There is a slight general diffuse sclerosis throughout the white matter of the cord in all regions, but in certain regions there is a perceptible naked eye combined sclerosis affecting the direct cerebellar and Gower's tracts, Goll's column and the crossed pyramidal tracts. The ascending degenerations are very observable, as *Figs. 4 and 5* shew in the cervical region. This is to be expected, because in this region all the fibres belonging to these tracts have taken up a definite position, consequently disappearance of the fibre and replacement by neuroglia tissue is more obvious to the naked eye, but microscopic examination in any part of the cord shews the outfall of fibres in these systems and their replacement by neuroglia.

The descending degeneration in the crossed pyramidal tracts is obvious to the naked eye, but, aided by a hand lens, is very evident in the lower lumbar and sacral regions *(Fig. 6)*. *Figs. 7 and 8*—Examination microscopically shews an outfall of fibre and replacement by glia tissue of the crossed pyramidal systems in any part of the course. The direct tract is much larger on one side than the other, and in the cervical region a well-marked outfall of fibres with sclerosis is observable with a low magnification. This is more obvious on the side where the direct tract is the larger. Some scattered sclerosis can be observed in the pyramids of the medulla.

CHANGES OBSERVED IN SECTIONS OF THE CEREBRUM, CEREBELLUM, PONS, MEDULLA, SPINAL CORD AND SPINAL GANGLIA CUT BY THE PARAFFIN METHOD, AND STAINED BY NISSL, POLYCHROME, GIEMSA, LOGWOOD, EOSIN AND VAN GIESON METHODS.

It may at once be said that in none of the sections examined was there any evidenee of meningeal or perivascular infiltration with lymphocytes or plasma cells or with polynuclear leucocytes. I mention this, firstly, because the terminal streptococcal infection had, therefore, not invaded the cerebro-spinal fluid, and could, therefore, as there was no inflammatory sign, account for the changes in the neurones. Moreover,

the absence of chronic meningo-encephalitis and myelitis, so characteristic of protozoal diseases, *e.g.*, malaria, in which the vessels may be filled with the organisms and yet no inflammatory perivascular and meningeal reaction is seen, so that it in no way disproves a protozoal origin of this disease; moreover, although all the changes are like those produced by a chronic toxæmia, yet the cause of that toxæmia has not been satisfactorily determined. Whether the two ulcers found in the intestines had any relation to a chronic toxic infection it is difficult to say. The combined sclerosis is not unlike that found in a pernicious anæmia which we know may be due to a streptococcal toxæmia.

By any one of the methods mentioned the following changes may be observed :—

All the posterior spinal ganglion cells shew in varying degrees a marked chromatolysis, swelling of the cell, disappearance of the Nissl granules, except at the periphery, and frequently eccentric position of the nucleus *(Fig. 9)*. All the anterior horn cells and their homologues in the medulla and pons shew varying degrees of perinuclear chromatolysis; in some instances the cells are so markedly swollen, and the nucleus is so eccentric, that it appears as if the cell were dead. There was a marked chromatolysis of the cells of Clarke's column.

The Betz cells of the cortex shewed similar changes but not so marked *(Fig. 10)*; likewise the cells of Purkinje; the pyramidal cells of the cerebral cortex did not appear to be markedly affected.

Wherever the nervous system was examined the cells which normally have a Nissl pattern seemed to shew a change in the nature of a disappearance of the granules partial or complete, without any evident changes in the vessels of an inflammatory nature to account for the same. Seeing that there is a combined sclerosis of the cord, obviously these changes could not be of quite recent origin, and, therefore, capable of being explained by the terminal generalisation in the blood of streptococci from the balanitis. Moreover, my experience tells me that the nerve-cell changes rather indicate a chronic toxæmia.

CHANGES OBSERVED IN THE CELLS BY BIELSCHOWSKY FIBRIL METHOD.

The anterior horn cells and the cells of Purkinje, also the Betz cells, but to a less degree, shew in varying degrees, in different parts of

a section and in various regions examined, fibril changes similar in character. Some cells shew hardly any fibrils, others a few, others appear quite normal, as if they had been attacked in different degrees of intensity by the poison. This is not an unusual condition of things in chronic toxic conditions affecting the nervous system. *Fig. 11* shews the changes in the cells of Purkinje. *Fig. 12* shews a group of anterior horn cells.

Comparison of these changes in the cells of Dr. Box's case with those of a pellagrous patient who died at the Abassieh Asylum—for the notes and material of which I am indebted to Dr. Pearson—shew that there is no essential difference. There is a combined sclerosis of the spinal cord more marked in the Egyptian case; there are the same changes in all the ganglion cells of the spinal cord and brain, and there are no signs of acute or chronic vascular or meningeal inflammatory changes. This case came from a district where the maize which the people had eaten was very bad. My assistant, Mr. Mann, has made a preliminary examination of this maize, and he finds that compared with sound maize there was a considerable diminution of phosphorised lipoids. It is possible that any impoverishment of diet, by which certain essential substances in the blood fall below the physiological minimum, may play a part in a degenerative process of the nervous system. Still, here we find these two cases of Dr. Box, in which diseased maize certainly could not have played any part in the production of degeneration of the nervous system, similar in histological details to those of a case which had come from a pellagrous district in Egypt, where unsound maize had been a staple article of diet. It seems that we must look for some other etiological factor as the essential cause of this disease, and we can but admire Dr. Sambon's enthusiasm and energy in the endeavour to shew the protozoal origin of this disease by its epidemiology.

I wish to express my indebtedness to my assistant, Mr. Charles Geary, for the photomicrographs and preparations.

REPORT OF EGYPTIAN CASE.*

By Dr. R. W. J. PEARSON.

Setabbhooha Abdalla, native woman, belonged to the Mudirieh of Menoufieh. Nationality, Egyptian; age, 30 years; religion, Moslem. Not addicted to alcohol or hasheesh. First attack: admitted 18th September, 1911: died 16th November, 1911. Bodily state on admission: height, 150 cm.; weight, 6 stone; nutrition, bad; temperature, 37·1° C.; facial expression, sad; eyes—pupils round, central and equal; both eyes react to light and accommodation; pulse—weak, small and quick, 120 per minute; heart—pulmonary sound accentuated, otherwise normal; tongue—clean and steady; lungs—slight rhonchi in right lung near apex; respirations—17 per minute; bowels—has diarrhœa. Extremities—pellagrous rash over dorsum of hands and back of forearms, over dorsum of feet, over the knees, and the backs of the elbows. Nervous system—reflexes; knee-jerks exaggerated; no ankle clonus nor Babinski; speech—she speaks in syllables, due to weakness; gait—affected, due to weakness; sleep—good. Mental—does not know the day nor date, she speaks fairly sensibly; says she came to Cairo for her illness; does not see visions nor hear voices.

19th September, 1911. The patient has a dull melancholic expression. She is very depressed. She is disconnected in time and space; does not know where she is, or what day or date it is. Her mental reaction is very slow, and she seems to have great difficulty in expressing herself. She is very confused and incoherent. Her physique is below the average and she is much emaciated. She has a pellagrous rash on the face, round the eyes, and across the nose, also on the hands and forearms, feet and legs, knees and elbows. She has a marked tenderness on pressure over the posterior nerve roots. Her tongue is denuded of epithelium, and her parotids are markedly thickened. Her lungs are sound. Her heart has a very feeble action and there are hæmic murmurs at the base. Her chest wall is sound. Her eyes react to light and on accommodation. Her knee-jerks are increased; no ankle clonus nor Babinski's sign. She denies hasheesh and alcohol, and there is no history of them. She says she is very poor and has eaten a lot of dhurra. There are no signs of syphilis. She has pellagrous diarrhœa, and is in a very weak condition. She is not suicidal.

* These Notes were not presented to the meeting.

11th October, 1911. The general condition of the patient has slightly improved. Mentally she is not so confused now, and her mental reaction is quicker than on admission. The pellagrous (black) rash over her nose and eyelids is beginning to peel off, also the rash on her hands and feet. She has a peculiar gait, very like the gait of paralysis agitans, without the tremors of that disease. Her head and shoulders stoop forward in a " hunchback " fashion. Her knees are flexed and she walks flat-footed. Her muscular system is wasted and weak, and the patient supports herself with the skeletal system and ligaments rather than the muscles. The diarrhœa is getting somewhat better. Her tongue is denuded of epithelium. The enlargement of the parotids persists. Her knee-jerks are still, and no ankle clonus nor Babinski's sign. She still has marked tenderness over the posterior nerve roots. Her eyes react to light and accommodation.

26th October, 1911. The pellagrous rash is reappearing in the elbows, but is completely peeled off from the face and hands, leaving a whitish inelastic skin. The patient is getting more shaky and unable to sit up. She has stomatitis; she says she is well and strong.

2nd November, 1911. The patient is helpless and depressed. She is chattering and incoherent; she is in a condition of typhoid pellagra.

16th November, 1911. The patient died this morning at 6 o'clock after prolonged exhaustion.

Extract from post-mortem Notes :—The post-mortem was done on the 16th November, 1911. Condition of body and external appearances—very emaciated, with black pellagrous rash on feet and hands, elbows, etc.: parotids markedly enlarged, and tongue denuded of epithelium; markedly anæmic. Calvarium—450 grms., thickened and dense. The brain was kept for examination later and was not cut at the post-mortem. The dura mater was a good deal thickened and was adherent to the calvarium so much so, that the brain had to be removed with the calvarium still in situ, and afterwards carefully separated from it. There was a distinct excess of cerebro-spinal fluid. The spinal cord below the medulla (where it is cut in removing the brain) had a lot of blackish-brown pigment in the membranes, which was granular to the feel. Heart—160 grms., pale, anæmic, flabby and somewhat atrophied; no organic lesions of the valves; no atheroma of the aorta or coronary arteries. Right lung—

300 grms.; some pearly old adhesions all along anterior border. At the base of the right lung a small cavity, necrotic in origin, was found; no signs of tubercle; congested at base. Left lung—some pearly old adhesions along anterior border and surface of lung; no signs of tubercle; congested at base. Liver—1,040 grms; anæmic, otherwise normal; gall bladder contained some blackish liquid bile; no gall stones. One bilharzia worm was found in the specimen of portal blood taken. Right kidney—100 grms.; somewhat hard and fibrous; capsule strips easily; pelvis congested. Left kidney—120 grms.; capsule strips easily; somewhat fibrous; pelvis congested. Spleen—170 grms.; very congested; soft and friable. Intestines—the small intestine in normal condition; the large intestine in condition of chronic colitis with denudation of epithelium and patches of marked congestion with ecchymises and artorization of blood vessels. The stomach dilated and thinned with denudation of epithelium. The intestines as a whole shewed the thinning and transparency typical of pellagra.

Special Notes.—The bladder had granular sandy patches of bilharziasis. The spinal cord was removed and preserved for examination. Cause of death—pellagra.

Discussion.

Dr. A. J. Chalmers: There are only a few things which I have to say, as I have only recently taken up the study of pellagra.

With regard to Dr. Sandwith's remarks, I should like to say that he is an authority for whom I have the greatest respect, and I am very sorry to find myself in the opposite house to him with regard to this deficiency theory.

I will lay before you the case of a small boy affected with pellagra in Egypt. We are told that the boy eats out of the same dish with the rest of the family, but the other members of the family have not got pellagra. This small boy was quite free from pellagra until he was taken down to see his grand-parents, who live in one of the pellagrous villages in the delta of the Nile. He went there at one of the secondary pellagrous seasons in November, and he began to shew pellagrous symptoms about two weeks after his return from such a visit. If we

assume that pellagra is due to a deficiency in food, why should not the rest of the family, eating the same food, develop the same symptoms? Consider also the number of well-fed individuals who are met with suffering from pellagra—persons in such good condition that one would have thought that if there was any food deficiency they could draw upon their own bodies for a supply of the required material.

I am sorry that I cannot support Dr. SANDWITH, though I could bring forward from Egypt many points apparently very strongly in favour of the maize theory, until they are examined.

Dr. BOX has given us an account of a case occurring in London, which he very kindly permitted me to see in St. Thomas's Hospital. There can be no doubt that this was a genuine case of pellagra. Dr. BOX has, however, said nothing about the food which the boy received when in the hospital. It is of course not the first case of pellagra in England, nor the British Isles. Pellagra has been recognised in these islands as far back as 1860, and certainly in one of the cases which Dr. SAMBON and I investigated in Scotland, the food was most excellent, though I admit that the person had peculiar habits of dietary. This patient was not a poor person, and though pellagra is generally found among poor people still it may occur among rich people. A man with an income of £2,000 a year cannot be called a poor man, but such a person can develop symptoms of pellagra.

I must congratulate Dr. BOX upon his excellent diagnosis, as there is a very real difficulty in recognising pellagra. We know that it is often missed, and we may have missed it ourselves, and therefore I congratulate Dr. BOX upon his diagnosis.

There is, however, a point which has impressed me, as I have travelled either with Dr. SAMBON or alone through Southern Europe and Egypt, and this is the frequency with which the complaint occurs among young children often in mild form; and I think, with Dr. SAMBON, that the disease is overlooked in young children because it is often so mild.

I have listened with attention to the interesting observations of Dr. MOTT. Only this afternoon I have been examining certain sections which Dr. SAMBON and I made comparatively recently from a case in Roumania, which was interesting because it was a case of acute pellagra in which death was probably due to pellagra. The patient died from a hæmorrhage on the posterior aspect of the lower cervical and dorsal

cords. The sections shew microscopical hæmorrhages in the posterior portion of the cord, and also very marked degeneration of the nerve cells, more particularly of CLARK'S column.

There is another feature which Professor MOTT has very rightly emphasised, viz., the lack of any reactive inflammation on the part of the tissues. Nowhere around these vessels can any perivascular infiltration be seen, nor is there any inflammatory reaction in the cord. There is a certain amount of increase in the neuroglia tissue in the cord, but no inflammatory reaction. I have not, as yet, examined the brain sections.

As to the etiology of the disease I cannot go into reasons here, but I do say that taking all points into consideration I have come to the conclusion that the disease is not directly due to maize. Neither the photo-dynamic theory, nor the insufficiency theory, will explain all the facts, and one is compelled to consider that the disease is of parasitic origin.

The relationship of the epidemiology of the disease to the habits and life history of certain biting flies, as demonstrated by Dr. SAMBON, is very remarkable. With regard to the simulidæ, I know that we can find none in the delta of the Nile, but we can find biting flies which are closely allied to that family in places where pellagra is endemic.

Dr. J. M. MACLEOD: I have little of importance to add to the most interesting and instructive paper to which I have just listened. Last spring I had the opportunity of seeing a number of cases of pellagra with Drs. SAMBON and CASTELLANI in the slopes of the hills in the neighbourhood of Rome. I saw that the disease was common among children, and that it appeared to affect the well-nourished as well as the delicate people, and there was no evidence that it was due to malnutrition.

The most constant symptoms, both in its clinical appearances and distribution, was the cutaneous eruption. It seemed to me to be largely the result of the actinic rays and sunlight, and the germ of the pellagrins appeared to be unusually sensitive to these rays. But there was evidently some other faction which rendered the skin so abnormally sensitive. It had not the clinical feature of an ordinary solar dermatitis, either acute or chronic in a healthy skin. The underlying factor which rendered the skin so sensitive to the rays seemed to me to be probably some toxin circulating in the blood.

Mr. CASIMIR FUNK: Of the many theories on pellagra which have been put forward in the last few years, I shall deal with two only, namely the photodynamic and the deficiency theories. The photodynamic theory, originated by RAUBITSCHEK and HORBACZEWSKI, has lead to some very interesting facts. They have found that certain fluorescent substances found in maize, when injected into white animals, render them sensible to light. The symptoms, however, although very pronounced in most cases, have hardly any resemblance to those in pellagra. Several objections can be made to this theory. The first objection is that the substances in question act only when injected and not when taken in food. The second objection is that pellagra was observed in negroes, who following this theory, ought to be spared by the disease. The third and final objection is that photodynamic substances could never be yet detected in the blood of the patients.

I have performed myself some experiments on this subject. I saw for instance that pigeons, white and black, can be kept in light without any damage on a maize diet. Even autoclaved maize seems to be an ideal food for them. Maize is so rich in beri-beri-vitamine that three to four grains of maize are able to cure a dying pigeon from polyneuritis. The explanation of this fact is, that pigeons never suffer from scurvy. On the other hand animals like guinea-pigs when fed on maize develop a disease which is considered by AXEL HOLST to be scurvy.

Since my article on Deficiency Diseases *(Journal of State Medicine, June, 1912)*, where I classified pellagra as a deficiency disease, many authors drew our attention to the similarity of the symptoms of pellagra and scurvy. SCHÜFFNER and KUENEN have found in a very large number of beri-beri patients a skin erythema, resembling closely pellagra. Many other observations followed referring to cases with mixed symptoms of pellagra, scurvy and beri-beri.

In any case there is no doubt that maize is lacking in scurvy substance, and this is the only fact which guides us in the investigation of pellagra. The difficulty is that we have not found yet any animal which shews, when fed on maize, symptoms resembling the disease in man; we are, therefore, confined for the present to experiments on man. To my mind two ways are at the present available for the investigation of pellagra. The first is the investigation of the scurvy-vitamine, which I hope will throw some light on the etiology of pellagra. The

second way is the study of the influence of diet on pellagra. Pellagra is a disease of poverty; the Italian statistics shew that along with better economical conditions of the population the disease steadily decreases. I am firmly convinced myself that an addition of 10 to 20 per cent. potatoes to the staple maize diet will practically eradicate the disease. These experiments ought to be performed now on a big scale, in order to ascertain whether pellagra is a deficiency disease or not.

Sir R. HAVELOCK CHARLES: It is merely a question of a fact that I desire to ask, and to it to call the attention of members generally. The fact has been stated that in a certain Hospital and Lunatic Asylum in the United States, with a population of 2,000 people, 8·4 per cent. who are lunatics, are affected with pellagra. There is a large staff in attendance—physicians, nurses, servants and employees—living in the same surroundings, having the same food and water supply, bitten by the same insects. Who had pellagra? 8·4 per cent. of the lunatics, not a single soul of the staff attendant on them being attacked. What is the reason? Let us suggest it. Say it is a case of deficient nutrition. You have that in the lunatics, for we know that lunatics are subject to tuberculosis, beri-beri, and other complaints,—no reason has been suggested for it, save that of malnutrition. The same fact has been stated to be true with regard to all the other lunatic asylums in the United States. Lunatics are affected—staff escape free. It is quite possible that the micro-organism attacks those whose vitality has been lowered. I merely suggest this. On my own part I desire to thank Dr. BOX very much and also Dr. MOTT, whose magnificent specimens were a great treat to look at.

I think, however, there was a slight contradiction in what Dr. MOTT stated. First he said the condition of the specimens shewed possibly a protozoal infection.

Dr. F. W. MOTT: I did not say that. I said there was no perivascular infiltration.

Sir R. HAVELOCK CHARLES: That therefore bears out the opinion of workers in the United States of America and Italy, which is, that the post-mortem condition shews nothing whatsoever suggestive of a protozoal infection, but rather points to a condition of deficiency of nutrition, though the ultimate cause of this be unknown at present.

Dr. F. M. SANDWITH : I quite agree with a previous speaker that great credit is due to Dr. BOX for diagnosing this case. I have seen people in other countries to whom I have lectured on pellagra (I hope it was not *because* of my lectures), who were quite incapable of recognising a case. If you are going, Sir, to ask Dr. BOX to make any postscript reply, I should like to ask him if he can throw any light on the food of his patient. Dr. BOX told me the only thing interesting about the case with regard to the food was that the boy was fond of pop-corn. I should like to know whether this boy had a large amount of pop-corn and whether popcorn is or is not made of maize. It is the first case, so far as we know, we have ever had at St. Thomas's Hospital. It is not the first case in the south of London, because a few years ago I saw a case in the Bethlem Royal Hospital. While visiting the wards I was asked to give an opinion on a skin eruption. From the condition of the tongue and knee-jerks I came to the conclusion that it was a case of pellagra. On investigation it proved that the girl had recently come from South Africa, and was accustomed to eat maize.

I should like to say that the great help we have had from Dr. MOTT to-night is not by any means the first assistance he has rendered to me in trying to elucidate the mysteries of pellagra. He has been kind enough to examine specimens I have at different times brought home from Cairo. Unfortunately the condition in which I brought the spinal cords and nerves never met with his approval, and he was not able to find everything which otherwise he might have been able to do.

I would like very much to ask Dr. MOTT if he can form any sort of idea in his mind as to what the probable cause of pellagra is. Is it a disease possibly due to deficiency of nutrition, like beri-beri, or an intoxication like ergotism, or is it a protozoal disease like malaria or sleeping sickness ?

Dr. SAMBON, who always carries me away with his eloquence, and almost persuades me to be a believer whenever we talk about pellagra, said that he thought of publishing a paper, of which he read to us a portion. I do not know why he says that usually writers have stated that children were not affected. I cannot understand that. Children have always been affected with pellagra in every country, and I have certainly seen many hundreds of cases in children under 10 years of age. You do not often get fatal cases among children. It is not rare to meet

it in young children, and that accounted for the old idea that pellagra was hereditary. The disease occurs in quite young children under two years of age.

I was interested in hearing Dr. FUNK's view that possibly the addition of potatoes to the diet might do away with early cases of pellagra; that would be a cheap and easy experiment to make.

Sir HAVELOCK CHARLES has been referring to the Peoria Asylum, which one has read about and discussed. In justice to Dr. SAMBON's theory, I would like to say that I asked that question of some of Dr. SAMBON's disciples, and they suggested that as at this lunatic asylum the lunatics have freedom, and there are no walls, etc., they wander about and get down to the streams, and they may thus possibly come more into contact with the aquatic insects, than the nurses, officials, and doctors, who have their work to do and cannot ramble so far afield.

Dr. C. R. BOX: One or two points I can throw a little light on. In the first place, Dr. SANDWITH asked about the duration of the second case. It was about four months in all from the first observed symptoms. The duration of the first case was six or seven years. We made as particular inquiries as we could with regard to the boy's food. We saw relatives, and wrote to the father, and he was emphatic that none of the children of the family had any different food, they all had the same diet and had plenty. He was certain that the boy's wasting was due to failing appetite. We examined several other members of the family. All these were quite well, all perfectly free from pellagra.

It is true that the boy was fond of popcorn, which I suppose is a form of maize, and both he and his brother when they had any pocket money, a halfpenny or a penny, spent it on popcorn, but they could not have got a great quantity. Whether it had anything to do with the disease or not I do not know, but it is very curious that this fact should occur in the case.

With regard to the pathological examination. There was another examination carried out. We took a large number of smears of the organs at the post-mortem and they were examined by several of us. We could not satisfy ourselves there was anything in these smears that we should be justified in shewing you as protozoa.

Dr. F. W. MOTT: I am glad to hear that Dr. CHALMERS has found similar changes to those I have described. Dr. CHALMERS mentioned the existence of hæmorrhages; I have also observed hæmorrhages, but inasmuch as they appeared to be quite recent, I associated them with the terminal streptococcal blood infection from which the boy had suffered. It would be interesting to examine the posterior spinal ganglion systematically to see if there was any correlation between the marked chromolytic changes of the cells of certain ganglion and the segments of skin affected with the rash. This necessitates a comparative microscopic examination of ganglia which innervate respectively healthy and affected skin areas. The changes I have described in the cells and fibres point to a toxic origin. As there was no perivascular cell infiltration the microscopic investigation did not support the protozoal origin of the changes in the nervous system. I am of opinion that as many cases like this suffer from diarrhœa, and since there were ulcers of the intestine, it is possible that a toxæmia might arise from this source. Again, we are not sure whether some deficiency of an essential bio-chemical substance in the blood may not be the cause of these degenerative changes in pellagra.

Dr. L. W. SAMBON, Dr. A. CASTELLANI, and Sir RONALD ROSS also took part in the discussion. It is hoped that Dr. SAMBON'S contribution may be given in the next issue of the TRANSACTIONS.

NOTES AND COMMENTS.

BUDDING AND OTHER CHANGES DESCRIBED BY SCHAUDINN FOR *E. HISTOLYTICA* SEEN IN A RACE OF *E. TETRAGENA*.

By S. T. DARLING.

SCHAUDINN and CRAIG have described peculiar changes in a pathogenic entamœba which have been figured by CRAIG and by HARTMANN. These changes, believed to be essential features in the propagation of the entamœba known as *E. histolytica*, are :—

(1) Reproduction by budding; consisting in the formation of daughter entamœbæ.

(2) Reproduction by sporulation. This is accompanied by changes in the nuclear chromatin. The nuclear area becomes widened, stains diffusely, and apparently chromatin diffuses out into the cytoplasm. The nucleus stains less sharply, appears to give up its chromatin to the cytoplasm, and then degenerates. Often the nucleus is expelled after having taken up a position on the periphery. Small buds appear on the periphery, ranging in size from 3μ to 7μ in diameter; these become separated, and later develop a colourless double outline, becoming brown in colour, and apparently undifferentiated in the interior. Buds of ectoplasm filled with chromidia, protrude, and are budded off from the parent body, which later disintegrates.

SCHAUDINN described these appearances from human material in which the number of individuals is always sparse, compared with that encountered in experimentally infected kittens.

These budding forms described by SCHAUDINN and CRAIG are very rarely encountered in man, but may be seen on certain occasions in large numbers in cats experimentally infected with *E. tetragena*. I have seen them also in small refractile trophozoites in surface sloughs from a fatal case of tetragena dysentery. These trophozoites were of the "small generation" type; they contained chromidia, and hæmatoxylin stained specimens displayed the nuclear characters of *E. tetragena*.

Recently, in experimentally infected kittens inoculated rectally with *E. tetragena*,* after the strain had matured, and at the time or just before encystment, when each nucleus had the characters of *E. tetragena*, i.e., a prominent karysome, there occurred peculiar changes in some of the trophozoites, both in dry and in wet-fixed films. These changes, as well as can be ascertained from SCHAUDINN'S description and from CRAIG'S and HARTMANN'S drawings, are identical with most of the changes noted by SCHAUDINN and CRAIG in the development of the spore-cyst perpetuating forms of *E. histolytica*. The kittens had been inoculated rectally with trophozoites from a case of dysentery in man, and upon the death of the first set of kittens a second set was inoculated, and so on, until the strain matured. The material shewing the bud forms was in the fourth remove at the time of the death of the kittens, i.e., when the strain had become mature or senile, reduced in size until it resembled *E. minuta*, when chromidia had appeared in every trophozoite, and a few cysts had appeared. In wet-fixed hæmatoxylin preparations the peculiar changes noted in some of the trophozoites were as follows :—

(1) The appearance of buds of different sizes on the periphery of the trophozoites in question. These buds were usually clear, and free from chromidia. Some, however, contained chromidia, and not infrequently a bud contained the nucleus.

(2) The extrusion of chromidia, nuclei, and portions of cytoplasm. Chromidia were seen, apparently being extruded. The nucleus always took up an extreme peripheral position in the cytoplasm, was frequently attached by a slim pedicle of cytoplasm, and later detached. Round portions of the cytoplasm (buds) were extruded.

The staining qualities of the nucleus in these forms was always less sharp than in trophozoites, and a few cysts, apparently normal, near by.

These findings can easily be confirmed by the rectal inoculation of kittens, and search made in material from the last remove containing trophozoites with chromidia.

* The strain is regarded as being a pure race of *E. tetragena*, for it was scrutinized from the patient through each remove, and in the third and fourth remove all trophozoites had the nuclear characters of *E. tetragena*, and the fourth remove contained a few *E. tetragena* cysts.

While a final opinion as to the significance of the changes cannot be given at this time, the staining reactions in wet-fixed films indicate that they are all degeneration forms of *E. tetragena*. A fuller report, with drawings, will appear later.

It is believed that these findings in the cat establish a correlation between the findings of SCHAUDINN and CRAIG on the one hand, and those of VIERECK, WERNER, HARTMANN, and others on the other, and it emerges that *E. tetragena* is the common pathogenic entamœba of man, as HARTMANN has already stated, and that "*E. histolytica*" is, in all likelihood, a spurious species, having been described from degeneration forms in senile races of *E. tetragena*.

THE NATURE OF ZAMBESI FEVER.

BY

W. J. BRUCE, M.R.C.S., VICENTI, ZAMBESI, PORTUGUESE EAST AFRICA.

I should like to submit to the Fellows the following notes in extension of the paper on the above subject, which was accepted by the Society and read on the 19th May, 1911, in which I pointed out that I thought a mistake had been made in assuming that Zambesi fever was malaria.

When I took over medical charge of a sugar estate on the lower river, employing from 500 to 2,000 recruited Kaffir labourers, in addition to a staff of a score of Europeans, and about a dozen Eurasians and negroes, I found that there were always a number of Kaffirs in hospital with fever, bowel complaints, and debilitating conditions of obscure nature, and when I had obtained a stock of thermometers and temperature charts, and trained the attendants to take temperatures, found that the two latter complaints were also associated with fever, so that it was no exaggeration to say that all our medical cases in hospital were fever cases.

The Kaffirs being in proportion to staff as fifty to one, at first one saw nearly all the cases among them, but I gradually came to the

conclusion that the staff suffered from the same forms of sickness, that it was all one disease against which the West Indian negroes were not protected as compared with the Europeans.

If this proves to be the case we may reasonably hope, in course of time, to devise prophylactic measures which will render the Zambesi valley a healthy district, but if the fever of that country is calmly assumed without proof to be malaria, there is a danger that not only will there be no improvement, but that anti-malarial measures may be discredited among laymen.

At the time of writing the paper, I had examined the blood of something over 150 fever patients, without finding parasites (I expected to find spirochætes), and I had not seen a decidedly malarial type of temperature curve, so I rashly suggested that the district was not really what is usually called malarial; but I admit now that I was misled by the protection given to Europeans by various forms of prophylaxis, and to Kaffirs by immunisation in childhood. The death-rate among children was very high, and when the Kaffir mothers knew me well enough to trust the infants to me I found that those with fever usually shewed the plasmodium malariæ.

This disposed of my doubts as to my own ability to detect the parasite. I have looked over some of these positive smears and again searched some of the negative smears since arrival in England, and feel confident that I did not pass as negative more than a very small percentage, if any, that contained the parasite. After sending off the original paper I examined 148 smears from Kaffirs, all taken before any quinine had been administered, and all admitted into hospital for fever, and not including casual examinations of out-patients. In two I found ring form parasites, but no crescents. Of 109 in which I made a leucocyte count, 50 shewed a large mononuclear proportion of over 12 per cent., 11 quite 20 per cent., and obviously an increase without counting. The two patients whose blood shewed the parasites were well in a day or two, and most of the others were much longer, and shewed no evidence of being affected by quinine. The quinine was given in a solution of the bisulphate ten grains to the ounce, which I made myself and frequently saw administered and swallowed. The shrinkage of the bottle was compared with the amounts ordered on the bed-cards, and I do not think my hospital attendant shirked that duty.

Another reason why I missed the malaria at first was that there were very few newcomers among the Europeans; but in 1911 a number arrived and lived in the place at the same time as about thirty coloured and three white Mauritians, who were new arrivals, and then it was interesting to note that among the Europeans there were several attacks of fever which shewed the malaria type of chart and quickly recovered on the exhibition of quinine, whereas among the Mauritians who usually treat fever at home with a dose of castor oil and a day in bed there were none, but that quite two-thirds of them went down one by one with the long fever that I call Zambesi fever.

One of them, who was ill a long time, was an old man, who told me that he had had no fever since he was a youth, and that what they had was quite a different sickness.

Dr. C. F. HARFORD'S remarks on the occasion of the reading of Sir W. LEISHMAN'S paper in October, reminded me how these people had said: "We have no fever like this in our country, Doctor!" and how indignant they seemed that they had been brought there under the impression that it was their old enemy from which they thought they were pretty thoroughly immune.

For the purpose of serum test, 24 specimens of blood were submitted to the bacteriologist at the Government laboratories, Johannesburg, of which four gave a definite and two a feeble reaction with mic. melitensis. Two of these samples were taken at an interval of about ten days from a European case I had diagnosed as not malaria, and probably undulent fever. Both were positive. The others were Kaffir cases. This patient went home to Switzerland when convalescent, and informs me he has never had any illness since then. He had suffered in a vague way for some month or two before he had to lie up.

All the Europeans who arrived in my time, to the best of my belief, took five grains of quinine bisulphate daily, or most days. Some were never ill, but many one day developed an attack of fever. They had usually taken an extra ten or fifteen grains before I saw them. One of two things happened; either the temperature was of the malaria type, or normal too soon to shew any type and the patient back to work in one to five days, or the fever lasted a long time and shewed no signs of being affected by quinine, and no mid-day rise nor two-day periodicity, but a regular evening rise as in phthisis.

This long fever often cleared up for a day or two and relapsed again, and with the onset of the relapse there was often diarrhœa and vomiting, but a noticeable point was that the vomiting occurred with a clean tongue and without nausea, which is quite unlike the condition in malaria. Some would eat with good appetite and vomit the whole contents of the stomach soon after. In malaria when there is vomiting the tongue is always coated and appetite lost.

That I failed to find malaria parasites in the blood of the European cases that were clinically malaria is not surprising, because they had all been taking quinine, and does not affect as evidence the fact that I failed to find them in the case of hundreds of Kaffirs where I obtained the smear before any quinine had been taken, at the same time that I was recognising them in the blood of Kaffir children, especially as the charts of those Kaffirs are not at all like malaria charts.

I do not know whether there is more than one non-malarial fever classed popularly under the name Zambesi fever, but I feel it my duty to impress on practitioners all over Africa, that in the lower Zambesi valley at the present day the important disease is not malaria, because we can so easily prevent and control that disease but this other fever, because we do not at present know its etiology nor how to treat it, and it is of such long duration and leads to a great deal of invaliding and a certain number of deaths.

I should like to add that in the early part of 1911, I had hardly any staff, white or native, to attend for about four months, so I carried out an experiment. I stopped my prophylactic quinine and in two months had an attack of fever, which shewed a temperature curve in which alternate days corresponded, the second, fourth and sixth being higher. I also noted that the fever increased gradually from early in the day and not abruptly in the evening.

On the fifth day I took ten grains of quinine bihydrochloride and observed no effect. On the sixth, twenty-five, and the fever ended abruptly, like that of lobar pneumonia. I continued a daily five grains (bisulphate) and had no recurrence.

I believe this attack was malaria, which reacted promptly to quinine, because I have a good resistance, the result of severe and repeated attacks years ago, before we understood much about the disease. But the Kaffirs would have a better resistance, and as a matter of fact the two in whose

blood I found parasites were cured in 48 hours, whereas the other cases mostly appeared to be unaffected.

Now I wanted to demonstrate a contrast. Here was a whiteman who tried to get malaria, satisfied himself that he had got it, and by the exhibition of ten and twenty-five grains of quinine brought it to an end with dramatic suddenness; and there were some hundreds of Kaffirs, dosed with 20 grains a day, going through a long and exhausting fever associated with lymphatic inflammation and nerve pains (probably the "malarial neuritis" that one hears of).

Can anyone assert that their fever was malaria in the face of negative blood examination?

Personally, I do not believe that those Europeans who die on the voyage home to England, after treatment by experienced practitioners in West Africa for prolonged fever, ever die of malaria, and feel convinced that a little careful observation of such cases would satisfy medical men in that part that they have to deal with the same disease which we call Zambesi fever on the east side.

THE ETIOLOGY OF BLACKWATER FEVER.

By A. G. NEWELL, M.D., D.P.H., Lahore.

I have read with much interest the paper (and the notes of the discussion thereon) on "The Etiology of Blackwater Fever," by Sir William Leishman, F.R.S.. and in view of the fact that he has called for "a free interchange of opinion on the debatable points," and this subject being one of the greatest importance to medical men practising in highly malarious districts, I should like to make the following remarks:—

On page 3 of the November, 1912, issue of the Transactions Sir William groups the various hypotheses as to the etiology into four groups. In my opinion, the first is the only one which represents the nearest truth, and the only one so far which has not been contraverted by unquestionable proof. To say that "undoubted cases have

occurred in which no evidence of malaria could be detected either before, during or after the paroxysm" is not conclusive evidence of the absence of a relationship to the disease; and if the malignant tertian parasite be regarded as the parasite concerned, it is not difficult to understand the difficulty in finding the parasite, both on account of its predeliction for internal organs and the great loss of corpuscles owing to hæmoglobinuria. To say "although parasites may be found in a very large majority of the cases, particularly on the day before the attack, there is no direct relationship between their numbers and the severity of the subsequent attack of blackwater fever," is insufficient without discriminating the variety of the parasites. I should like to know who has shewn that a large number of malignant tertian parasites have been found the day before the attack of blackwater fever, and in how many cases, and the relationship of the numbers of the parasites to the severity of the attack. Here I should like to add that the severity of the attack need not depend upon the numbers of the parasites found, because I am of the opinion that the severity of the attack—and even the attack itself—is dependent upon the degree of malignancy possessed by the parasite itself. This is supported by the fact observed by me that even in the same district the malignant tertian parasite will not always produce the same degree of severity of symptoms, and whilst I admit several other factors, such as the habits of the individual, regularity of his quinine taking, and the dose used may affect this, yet it is an outstanding fact that some parts of the same district give severer cases; whilst malignant tertian cases were common in one district I worked in, there was one house in which during seven years there were six deaths of Europeans from blackwater fever, and the Europeans themselves took in most cases extra precautions. But the situation of the house itself was such that ideal conditions existed for anopheles breeding, etc. It was only after my condemnation of the site, and some trouble, that a new house was erected on a healthier site. In another district, where I myself got the disease, the end of the district where I lived gave the majority of the severe malignant tertian cases and blackwater fever. Then it is said that "The theory that blackwater fever may be due to the malignant tertian parasite alone has been disproved, since it has been found, though rarely, associated with both quartan and benign tertian." I contend that because quartan and benign tertian parasites have been found in the

peripheral blood of blackwater fever cases *rarely* is no evidence whatsoever that the malignant tertian parasite is not the cause of the disease, since this parasite is found with difficulty in the peripheral blood in such cases (for the reasons already stated), and both quartan and benign tertians would be more commonly found were it not for the great destruction of blood corpuscles. There is no reason why the three parasites should not co-exist in the case, and in such cases I would rather expect to find them than the reverse but for the great dissolution of corpuscles. I disagree entirely that an attack is uninfluenced by quinine, and this has not been my experience. I consider that no evidence is forthcoming to dispute the view I have put forth (in my book on "Blackwater Fever") as to the relationship of the malignant tertian parasite to blackwater fever. All malignant tertian infections of a certain degree of virulence would, untreated by quinine, in time tend to death or hæmoglobinuria.

Re quinine as a cause. Quinine, of course, could not be a *cause*. There is no reason why quinine should not induce an attack in one severely infected with malignant tertian parasites at a time when the liver is extremely congested (it follows that quinine has been neglected or the severe infection could not have occurred). This might recur in the same individual more than once under the same conditions. It does not follow because one dose induced the attack under the above conditions that large doses subsequently would induce—on the contrary, the large subsequent doses would prevent the development of the parasites.

Re the third view—that of a specific organism. If such was the case we would expect more cases in the same district. There is nothing to support this view. New-comers should be more prone to the disease.

Re the fourth view, viz., that "it is a result of a condition brought about by previous malarial infection." It is agreed that "there is a close and constant association with malaria." This association, in my opinion, is related to the malignant tertian parasite, and the condition which brings about the hæmoglobinuria is the intense congestion of the liver. If the condition of the liver is looked to before quinine taking, and during residence in intensely malarial districts, together with regular taking of sufficient quinine, there should be no blackwater fever. The existence of blackwater fever in districts previously unknown to have such cases may be attributed to (1) the particular virulent parasite being taken into the district by persons harbouring the parasite in their

internal organs; (2) the great use of tablets of quinine in recent years, which, in many cases, contain insufficient amount of quinine or from stocking (from large quantities having been ordered) are undissolved in the stomach. Quinine, to be valuable, should preferably be given in solution or intramuscularly.

Nothing in the above views interferes with my agreement with the views of DEEKS and JAMES recapitulated on p. 7 of the November issue. I draw attention to No. 3, p. 8, as giving great support to my view as to the relationship of the malignant tertian parasite and the disease.

Re the fairly well established points, summarised on p. 10, I agree with (1), (2) and (3). With regard to (4), I agree with the statement, "the regions of most intense malarial infection are those in which blackwater fever occurs." I will not pin myself to the latter part of the sentence, viz., "but there exist also extremely malarious regions in which it is either extremely rare or absent," because the hæmoglobinuria is only a symptom of a malignant tertian infection, and it is possible to be absent, or blood may be passed into any part of the intestinal tract, and even if not missed may not be regarded as blackwater fever. With regard to (5):—Whilst I agree that cold and quinine may be exciting factors, I do not agree that an exciting factor, beyond the congestion of the liver, is necessarily required. *Re* (6):—I agree that the precise mechanism of the hæmolyces is not fully understood, but disagree with the remainder of the evidence, and am of the opinion there is a direct relationship to the intensity of the parasite.

The cell inclusions discovered by Sir WILLIAM are most interesting and deserve further attention. They may be a variety of the malignant tertian parasite which causes blackwater fever.

Dr. F. M. SANDWITH says: "The suggestion that hæmoglobinuric fever is a complication of malaria must not be put aside because it is not to be cured in the same way as malaria." This statement I consider requires emphasizing, because when nature has asserted herself by clearing the blood of the parasites of the sudden hæmolysis, it is rather late to expect quinine to act then as it would well before the blood infection reached so intense a stage.

I agree with Dr. A. J. CHALMERS that there is a quinine hæmoglobinuria and a malarial hæmoglobinuria. Small doses of quinine are of little use in the prevention of malignant tertian infections in intensely

malarial districts, and I see no reason why a man who has not sufficiently protected himself by adequate doses should not develop more than one attack of blackwater fever (with hæmoglobinuria) and live—none of the attacks being of sufficient intensity to kill him.

THE ETIOLOGY OF BLACKWATER FEVER.

By H. STANNUS STANNUS, M.D., Nyasaland.

I have just received the number of the *Transactions* containing notes and comments on the etiology of blackwater fever, and beg to make the following remarks as a practitioner in East Central Africa (Nyasaland).

With some eight years experience in this country, I have never seen a case of blackwater fever in a native, though it is a disease which may be called "prevalent" in some districts among Europeans; Indians also being attacked.

I believe all medical men here have had the same experience.

With Sir William Leishman's pronouncement "immunity to malaria appears to go hand in hand with immunity to blackwater fever, and measures which protect against malarial infection are also prophylactic against blackwater fever," I am in agreement, though the so-called immunity of the native population should be a qualified statement. It is not an immunity to infection, but an immunity in adult life to the severe manifestations of the disease.

I think, undoubtedly, hæmaturia (from bilharzial infection which is very common in this country), may have been responsible for some of the old fables of the occurrence of blackwater fever among natives of East Africa.

I have often thought this might account for the use of cassia beareana in the treatment of blackwater fever.

My experience leads me to believe "no malaria, no blackwater fever." I have seen no case in which there has not been an antecedent history of malaria and of taking quinine, I think in every case the sulphate immediately before, that is to say within a few hours of the attack.

In contradiction to Dr. Chalmers' ideas I may add that I have attended several men in two attacks of blackwater fever and know of several others who have had three and four attacks.

EDITORIAL NOTICES.

The Editor of the TRANSACTIONS will be pleased to receive short papers to be included under the heading of "Notes and Comments or "Questions," in addition to longer papers on subjects of Tropical interest, which may be offered for presentation at meetings of the Society. He will also be glad to receive books for review.

Any communications for the Editor should be addressed to THE EDITOR of the TRANSACTIONS of the Society of Tropical Medicine and Hygiene, 11, Chandos Street, Cavendish Square, W

NOTICES OF MEETINGS.

The next Ordinary Meeting of the Society will be held at 11, Chandos Street, Cavendish Square, W., at 8.30 p.m., on Friday, April 18th, 1913, when—

1. A Paper will be read upon "Sanitation in the Tropics, with special reference to the Panama Canal Zone, Trinidad and British Guiana," by Dr. DAVID THOMSON, of Liverpool.

2. A Demonstration on "The Cultivation of the Malarial Parasite outside the Body," will be given by Dr. J. G. THOMSON, of Liverpool.

3. A Paper will be read on "Observations on the Cultivation of the Malarial Parasite and of Piroplasma canis," for Professor H. ZIEMANN.

ELECTION OF FELLOWS.

The following were duly elected Fellows of the Society :—

Lieut.-Col. HUBERT A. BRAY, M.R.C.S., R.A.M.C., Khartoum.

JOHN J. W. EVANS, F.R.C.S., Westminster Hospital.

FREDERICK A. SAUNDERS, F.R.C.S., South Africa.

WILFRID THUNDER, M.B., Perak.

EXCHANGES.

Annali di Medicina Navale e Coloniale.
Archives de l'Institut Pasteur Tunis.
Archives fur Schiffs und Tropenhygiene.
Archivos do Real Instituto Bacteriologico Camara Pestana.
Bulletin Public Health and Marine Hospital Service of the U.S.
Bulletin of the Sleeping Sickness Bureau.
Bulletin de la Société de Pathologie Exotique.
Bulletin de la Société Portuguaise des Sciences Naturelles.
Bulletin de l'Academie Royale de Médecine de Belgique.
het Geneeskundig tydschrift voor Nederlandsch-Indie.
Indian Civil Veterinary Department Memoirs.
Johns Hopkins Hospital Bulletin.
Journal of Meat and Milk Hygiene.
Journal of Tropical Veterinary Science.
L'Enseignement Medico Mutuel Internationale.
Memorias do Instituto Oswaldo Cruz.
Philippine Journal of Science.
Revue de Médecine et d'Hygiene Tropicales.
Sanidad y Beneficencia.
Veterinary News.

NOTE.—The above publications lie on the Library table at 11, Chandos Street, and are at the disposal of Fellows.

J. C. PHELP AND SON, PRINTERS, WALTHAMSTOW

PUBLISHING NOTICES.

NOTICE TO FELLOWS.

A copy of the "Transactions" will be posted regularly to every Fellow whose subscription is not in arrears during the Session.

Fellows are requested to give early intimation of any change of address, and in case of non-delivery of their copies of the "Transactions," to communicate with the Secretaries as soon as possible. When copies of the "Transactions" are returned by the Post Office, marked "gone away" or "insufficiently directed," no more copies will be posted to that address until further instructions have been received.

All communications should be addressed to—

THE SECRETARIES,
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11, CHANDOS STREET, CAVENDISH SQUARE, W.

SALE OF COPIES TO NON-FELLOWS.

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Fellows of the Society are reminded that they can only obtain their copies through the Secretaries, as stated above, and not from MR. LEWIS.